REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 1, 2, 4-17 are in this Application. Claims 4-11 have been withdrawn from consideration. Claim 13 is allowed. Claims 1, 2, 12 and 14-17 have been rejected under 35 U.S.C. § 112, first paragraph. Claims 14-17 have been rejected under 35 U.S.C. § 112, second paragraph. Claims 15-17 have been rejected under 35 U.S.C. § 103(a). Claims 14-17 have been cancelled herewith.

35 U.S.C. § 112, first paragraph Rejections

The Examiner has rejected claims 1, 2, 12 and 14-17 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

Specifically, the Examiner states that claim 1 has been amended to recite "wherein all of said plurality of complexes are recognizable by one CTL clone" in an attempt to differentiate the claimed invention from the prior art and that the cited text by Applicant does not germane to the amendments to the claims and that in Figures 3a-b there is no disclosure of a plurality of complexes that are all the same and no disclosure of binding to the same CTL, the Figures merely depict a protein band of a single size. The Examiner's rejections are respectfully traversed. Claims 14-17 have been cancelled, rendering moot the Examiner's rejections with respect to these claims.

Applicant points out that the present invention is of a plurality of complexes (each composed of an antigenic peptide being capable of binding a human MHC class I, and a chimeric polypeptide which comprises a functional human β-2 microglobulin translationally fused to a functional human MHC class I heavy chain) which are all recognizable by one CTL clone.

The presence of a plurality of complexes which are all the same (and therefore inherently recognizable by a single CTL clone) is supported by their mode of preparation, essentially the bacterial expression of the chimeric polypeptide (from the single chain MHC construct) and refolding of the resulting chimeric polypeptide in the presence of an antigenic peptide (see Citation I, hereinbelow). The resultant population of complexes is a homogenous population (see Citation II, hereinbelow). Figures 3a-b and its description depict the purified homogenous scMHC-peptide

complexes of the present invention as single protein bands. Evidence for the recognition of the plurality of MHC-complexes by one CTL clone is provided, for example, by the description of the experiment in which the scMHC-g9-209-2M complexes were tested for their ability to induce CTL activation, in which a specific activation of the g209-specific CTL clone R6C12 by the homogenous population of monomeric molecules of scMHC-peptide complexes was observed (see Citation III, hereinbelow).

Citation I: Page 42, lines 3-18

"the scMHC constructs subcloned into pET21 were expressed ... forming intracellular inclusion bodies in BL-21 DE3 cells. ... inclusion bodies were refolded ... in the presence of ... antigenic peptides.... Soluble scMHC-peptide complexes were purified ...."

Citation II: Page 47, lines 17-22 – Page 48, lines 1-15

"Refolded complexes were dialyzed and concentrated following by purification.... SDS-PAGE analysis, under non-reducing conditions, of refolded purified scMHC-peptide complexes revealed a homogenous monomeric population of molecules that migrated as a uniform single band corresponding to the scMHC molecule... As shown in Figures 3a-b, purified homogenous scMHC-peptide complexes were obtained with all three peptides tested. When the scMHC was refolded in the absence of a peptide, a highly aggregated protein was observed which was composed of a heterogeneous population of molecules .... Thus, a uniform population of monomers could only be found in the peptide-induced refolding preparations...." (Emphasis added)

Citation III: Page 52, lines 21-23 – Page 53, lines 1-5

"The recombinant purified scMHC complexes that were produced with the 3 different peptides (G9-209-2M, G9-280-9V, and TAX) were immobilized on a microtiter plate and tested for the ability to induce CTL activation. As shown in Figure 7a, the single-chain MHC molecule bound to the g9-209-2M peptide induced specific activation of the g209-specific CTL clone R6C12 as determined by interferon-g levels. On the other hand, the complexes bound to the g280 and TAX peptides did not induce specific activation." (Emphasis added)

Thus, the above remarks and citations demonstrate that the plurality of MHC-peptide complexes of the present invention are all recognizable by one CTL clone which is specific for the antigenic peptide of the MHC-peptide complex.

The Examiner further states that new claims 14-17 each recite the term "monomeric complex(es)" and that the citations provided by Applicant do not germane to the amendments to the claims. The Examiner's rejections are respectfully traversed. Claims 14-17 have been cancelled. Applicant points out that the instant application provides ample support for the term "monomeric complex(es)". For example, as described in citation II, hereinabove, "*refolded purified scMHC-peptide complexes revealed a homogenous monomeric population of molecules*". It is clear that the word "molecules" in this sentence refers to the "scMHC-peptide complexes", thus supporting the term "monomeric complexes".

Notwithstanding the above and in order to expedite prosecution of this case, Applicant has elected to cancel claims 14-17, to thereby overcome the Examiner's rejections with respect to these claims.

In view of the above arguments, remarks and claims cancellations, Applicant believes to have overcome the 35 U.S.C. § 112, first paragraph rejections.

35 U.S.C. § 112,second paragraph Rejections

The Examiner has rejected claims 14-17 under 35 U.S.C. 112, second paragraph, as failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, the Examiner states that claims 14-17 are each ambiguous and unclear in the recitation of "monomeric complex(es)" and that the term is not disclosed or defined in the specification. The Examiner further states that a monomer is generally accepted in the art as being a singular polypeptide molecule, while a complex is an association of at least two polypeptide molecules. The Examiner's rejections are respectfully traversed. Claims 14-17 have been cancelled herewith, rendering moot the Examiner's rejections with respect to these claims.

Applicant would point out that the term "monomeric complex" is well known and accepted in the art to describe protein complexes which exist in a monomeric form (*i.e.*, when the protein complex does not associate with additional protein complexes). The presence of monomeric complexes can be confirmed by protein gel electrophoresis (e.g., SDS-PAGE) under non-denaturing and/or non-reducing conditions which retain the associations between proteins as exist in their natural form. For example, in the instant application the presence of the monomeric

complexes of human MHC-peptide was confirmed by the non-reduced SDS-PAGE (see Figures 3a-b, description of Figures 3a-b on Page 15, lines 17-22 – Page 16, lines 1-4; and Page 47, lines 19-22 – Page 48, lines 1-2).

Applicant point outs that the term "monomeric complexes" was widely used in the art to describe monomers of the mitochondrial protein complexes (See for example, Schagger H., 2001, enclosed herewith), monomers of the nuclear pore complex (e.g., Nup84p complex which is composed of 5 nucleoproteins as described in Siniossoglou S., et al., 2000, enclosed herewith), and monomers of ligand-receptor complexes (Layton JE et al., 2001, enclosed herewith).

Notwithstanding the above and in order to expedite prosecution of this case, Applicant has elected to cancel claims 14-17, thereby rendering moot the Examiner's rejections with respect to these claims.

In view of the above remarks, arguments and claims cancellations, Applicant believes to have overcome the 35 U.S.C. § 112, second paragraph rejections.

35 U.S.C. § 103(a) Rejections

The Examiner rejected claims 15-17 under 35 U.S.C. § 103(a) as being unpatentable over Mottez et al., (J. Exp. Med. 1995, 181 : 493-502) in view of Lone et al. (J. Immunotherapy, 1998, 21 : 283-294).

Specifically, the Examiner states that Mottez teaches single chain constructs comprising a murine MHC class I heavy chain joined to β2-microglobulin with a covalently bound antigenic peptide. Mottez teaches that linker, or spacer, sequences separate the segments. The Examiner further states that Mottez does not specifically teach human MHC class I heavy chain or β2-microglobulin. However, in continuation of the same work, Lone teaches that the same techniques were applied to human MHC class I heavy chain HLA-A2.1, which was joined via a 15-amino acid linker to human β2-microglobulin, and that Lone teaches that the single chain MHC class I construct folded properly and was functional. In addition, the Examiner states that Lone teaches that the single chain MHC class I construct specifically bound HLA-A2 restricted peptides and induced peptide-specific cytotoxic T cells to proliferate and produce IL-2 and that since the Applicant's meaning of "monomeric complexes" is not defined in the specification and is therefore ambiguous, it is believed that the single chain MHC class I molecule of the combined references satisfies the metes and

bounds of being a monomeric polypeptide complexed with an antigenic molecule. The Examiner's rejections are respectfully traversed. Claims 15-17 have been cancelled herewith, rendering moot the Examiner's rejections with respect to these claims and overcoming the 35 U.S.C. § 103(a) rejections.

In view of the above amendments and remarks it is respectfully submitted that claims 1, 2 and 12 are now in condition for allowance. A prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,

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Encl.:

References:

Schagger H., 2001; IUBMB Life. 52(3-5): 119-28 (Abstract);

Siniossoglou S., et al., 2000, J. of Cell Biology, 149: 41-53 (full manuscript);

Layton JE et al., 2001, The J. of Biological Chemistry, Vol 278: 36779-36787 (full manuscript);

1: IUBMB Life. **2001 Sep-Nov;52(3-5):119-28. Links**

Respiratory chain supercomplexes.

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Respiratory chain supercomplexes have been isolated from mammalian and yeast mitochondria, and bacterial membranes. Functional roles of respiratory chain supercomplexes are catalytic enhancement, substrate channelling, and stabilization of complex I by complex III in mammalian cells. Bacterial supercomplexes are characterized by their relatively high detergent-stability compared to yeast or mammalian supercomplexes that are stable to sonication. The mobility of substrate cytochrome c increases in the order bacterial, yeast, and mammalian respiratory chain. In bacterial supercomplexes, the electron transfer between complexes III and IV involves movement of the mobile head of a tightly bound cytochrome c, whereas the yeast S. cerevisiae seems to use substrate channelling of a mobile cytochrome c, and mammalian respiratory chains have been described to use a cytochrome c pool. Dimeric ATP synthase seems to be specific for mitochondrial OXPHOS systems. Monomeric complex V was found in Acetobacterium woodii and Paracoccus denitrificans.